ADDICTION
SSA SOCIETY FOR THE STUDY OF ADDICTION
RESEARCH REPORT
doi:10.1111/add.14552

Pharmacokinetics of a novel, approved, 1.4-mg intranasal naloxone formulation for reversal of opioid overdose—a randomized controlled trial

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ABSTRACT

Background and aims Intranasal (i.n.) naloxone is an established treatment for opioid overdose. Anyone likely to witness an overdose should have access to the antidote. We aimed to determine whether an i.n. formulation delivering 1.4 mg naloxone hydrochloride would achieve systemic exposure comparable to that of 0.8 mg intramuscular (i.m.) naloxone. **Design** Open, randomized four-way cross-over trial. **Setting** Clinical Trials Units in St Olav's Hospital, Trondheim and Rikshospitalet, Oslo, Norway. **Participants** Twenty-two healthy human volunteers, 10 women, median age = 25.8 years. **Intervention and comparator** One and two doses of i.n. 1.4 mg naloxone compared with i.m. 0.8 mg and intravenous (i.v.) 0.4 mg naloxone. **Measurements** Quantification of plasma naloxone was performed by liquid chromatography tandem mass spectrometry. Pharmacokinetic non-compartment analyses were used for the main analyses. A non-parametric pharmacokinetic population model was developed for Monte Carlo simulations of different dosing scenarios. **Findings** Area under the curve from administration to last measured concentration ($AUC_{0\text{-last}}$) for i.n. 1.4 mg and i.m. 0.8 mg were 2.62 ± 0.94 and 3.09 ± 0.64 h × ng/ml, respectively ($P = 0.33$). Maximum concentration (C_{max}) was 2.36 ± 0.68 ng/ml for i.n. 1.4 mg and 3.73 ± 3.34 for i.m. 0.8 mg ($P = 0.72$). Two i.n. doses showed dose linearity and achieved a C_{max} of 4.18 ± 1.53 ng/ml. T_{max} was reached after 20.2 ± 9.4 minutes for i.n. 1.4 mg and 13.6 ± 15.4 minutes for i.m. 0.8 mg ($P = 0.098$). The absolute bioavailability for i.n. 1.4 mg was 0.49 (±0.24), while the relative i.n./i.m. bioavailability was 0.52 (±0.25). **Conclusion** Intranasal 1.4 mg naloxone provides adequate systemic concentrations to treat opioid overdose compared with intramuscular 0.8 mg, without statistical difference on maximum plasma concentration, time to maximum plasma concentration or area under the curve. Simulations support its appropriateness both as peer administered antidote and for titration of treatment by professionals.

Keywords Administration, antidotes, drug overdose, intramuscular adminisration, intramuscular drug overdose, intranasal administration, intravenous administration, naloxone, narcotic antagonists, substance-related disorders.

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Submitted 14 September 2018; initial review completed 1 November 2018; final version accepted 4 January 2019

INTRODUCTION

The increasing number of deaths from opioid overdoses is extensively documented [1–3]. Opioid overdoses are reversed by naloxone. The maximum recommended initial dose of naloxone is 2.0 mg, but starting doses of 0.4–0.8 mg intramuscularly (i.m.) are favoured. The World Health Organization (WHO) guideline of 2014 warns that starting doses exceeding 0.8 mg may increase the risk of triggering acute opioid withdrawal [2]. Acute opioid withdrawal is rarely fatal, but is harmful to patients. Withdrawal may hinder the further medical and social follow-up required by these patients. Restoring ventilation and oxygenation, as well as careful titration of naloxone without overshooting the mark, are the goals of naloxone reversal [4,5]. The lowest safe naloxone dose should be

administered initially, with rapid escalation as warranted by the clinical situation [6].

Originally initiated by activist organizations, the distribution of naloxone to lay people has now become an important public health-care strategy [7]. Intranasal (i.n.) naloxone has been preferred due to its simple administration and reduced risk of exposure to blood. After years of using various off-label, improvised naloxone formulations without marketing authorization, several i.n. naloxone formulations are now licensed in Europe and the United States. They are all low-volume/high-concentration, and are characterized by absorption rates that deliver systemic exposure within the recommended range in one actuation.

In this setting—treatment of a life-threatening condition where titration is the cornerstone— pharmacokinetic (PK) knowledge of the formulation used is important to optimize dosing. The previous use of various dilute naloxone formulations given i.n. in improvised devices has been criticized [8,9]. Dilute take-home naloxone (THN) formulations typically have low bioavailability, ranging from 0.10 to 0.15 [10,11]. The corresponding dose absorbed of a 2.0 mg dose would then be 0.2–0.3 mg: 50–75% of the lowest recommended starting dose (McDonald *et al.*, unpublished). The off-label use of i.n. naloxone was the only alternative until the Food and Drug Administration (FDA) approved the Narcan 40 mg/ml nasal spray in 2015, with later additions to the market, both in the United States and Europe.

Other approved i.n. sprays (Narcan Nasal® and Nyxoid®) both deliver systemic exposure of naloxone higher than 0.8 mg i.m. There are two reasons for the development of high-dose i.n. sprays. In order to receive regulatory approval, the FDA has required that administration forms alternative to 0.4 mg i.m. must demonstrate similar or higher blood concentrations, especially in the initial absorption phase [12]. There is also concern that the naloxone doses that worked in the past may be insufficient, as the opioid epidemiology changes with the introduction of potent synthetic opioids such as fentanyl [13,14]. A meeting at the FDA in 2016 narrowly voted to increase the minimum acceptable naloxone exposure from 0.4 mg [15]. The 0.8-mg naloxone comparator is the higher spectrum of the WHO recommendation, and provides increased safety for successful reversal without sparking avoidable acute withdrawal.

The present study was conducted to demonstrate that a novel formulation delivering 1.4 mg naloxone hydrochloride would achieve systemic exposure comparable to that of 0.8 mg i.m. The i.n. dose was chosen on the basis of previous studies with the same formulation [16–18].

The formulation contains the stabilizer ethylenediamine tetraacetic acid (EDTA), the mucoadhesive substance povidone and the humectant glycerol. The licensed product will be delivered with two sprays per pack for dose titration.

MATERIAL AND METHODS

This study was a two-centre randomized, open label, four-way cross-over trial in healthy human volunteers, with 72 hours' wash-out.

It was approved by the Regional Committee of Medical and Health Research Ethics (2015/1285) and by the Norwegian Medicines Agency (EudraCT number: 2015–002355-10). All procedures were in accordance with the ethical standards of the Helsinki Declaration and the ICH Good Clinical Practice guidelines. The study was registered in clinicaltrials.gov (NCT02598856). Participants were insured through the Drug Liability Association, Norway, and compensated for each treatment visit with 1000 NOK (110 €/120 US$). The trial was conducted at Clinical Trials Units at St Olav's Hospital, Trondheim and at Rikshospitalet, Oslo, Norway between 28 October 2015 and 30 September 2016. The Smerud Medical Research Group operated as the clinical contract research organization.

The primary pharmacokinetic outcome variables were: area under the plasma concentration versus time curve (AUC) from administration to last measured concentration ($AUC_{0\text{-last}}$), AUC from administration to infinity ($AUC_{0\text{-inf}}$), maximum plasma concentration (C_{max}) and time to C_{max} (T_{max}), compared for single-dose i.n., i.m. and intravenous (i.v.) naloxone. Secondary outcome variables were dose proportionality, by comparing systemic exposure following one and two doses of 1.4 mg of i.n. naloxone, and absolute and relative bioavailability.

Eligibility criteria for participants

Healthy men and women aged 18–45 years with haemoglobin, creatinine, aspartate transaminase (AST), alanine transaminase (ALT) and gamma glutamyl transferase within reference values and a normal electrocardiogram (ECG) were eligible for inclusion. Regular use of medications, including herbal, were not permitted. Female participants required a negative pregnancy test, the use of high-efficacy contraception from inclusion and could not be breastfeeding during the study period. Participants with a history of previous nasal surgery, a history of drug allergies or drug addiction were excluded. A full list of inclusion and exclusion criteria is presented in the Supporting information.

Interventions

There were six study visits: first a screening visit for consent and eligibility criteria and lastly for safety follow-up. The four visits in between involved the administration of study medicine. All participants were set to receive all treatments. Treatment A comprised a single dose of i.n.

naloxone 1.4 mg, administered as 0.1 ml 14.0 mg/ml (1.4 mg naloxone HCl) by an Aptar Unit dose device as one puff in one nostril. Treatment B comprised a double dose of i.n. naloxone 1.4 mg, administered as 2 × 0.1 ml 14.0 mg/ml (2.8 mg naloxone HCl) by an Aptar Unit dose device as two puffs in the same nostril, 3 minutes apart. Treatment C comprised i.m. naloxone 0.8 mg, administered as 2.0 ml Naloxon B. Braun 0.4 mg naloxone HCl/ml in the deltoid muscle. Treatment D comprised i.v. naloxone 0.4 mg administered as 1.0 ml Naloxon B. Braun 0.4 mg naloxone HCl/ml. Adverse events were monitored at all visits. All participants underwent anterior rhinoscopy at the screening and the follow-up visit.

Randomization

This was performed by a computerized procedure from the clinical research organization Smerud, using block randomization without stratification. Subjects were randomized to the treatment order of the four naloxone administrations.

Study procedures

Participants were reclined fully as they received naloxone. They were monitored with oxygen saturation, ECG and non-invasive blood pressure. Participants who had taken any concomitant medication during the study period had their treatment visit re-scheduled to a time where at least five half-lives of the medication had passed, or a minimum of 7 days if no half-life was known.

Blood samples were drawn within 10 minutes prior to administration of naloxone, and then at 2, 5, 10, 15, 20, 25, 30, 35, 45, 60, 90, 120, 240 and 360 minutes after administration of study drug from an i.v. cannula placed in the antecubital fossa. Six ml blood was collected in glass tubes with K_2 EDTA anti-coagulant, gently mixed and centrifuged for 20 minutes at 1300 ***g***, and 0.5 ml plasma was decanted into cryotubes, immediately frozen at −20°C, and stored at −80°C before the end of the day and until analysis.

Naloxone analysis

A total of 1320 (88 sessions) plasma samples were to be analysed for naloxone using liquid chromatography tandem mass spectrometry. Only subjects contributing with data sets from all visits were included in the statistical analyses. Twenty-one plasma concentrations were missing, and these were not replaced. Of the 1299 measured plasma concentrations of naloxone, 161 were below the limit of quantification (LOQ) and one was above the upper limit of the calibration curve. The latter was set at 47.6 ng/ml and included in the analysis. Results below LOQ were not included in the analyses. Two concentrations measured before dose administration showed values above LOQ, and these two were set to zero in the analyses. In total, 182 (7.3%) were either below LOQ or missing, thus a total of 1138 plasma naloxone concentration measurements were used in the analyses.

The bioanalyses were performed by Vitas AS (Oslo, Norway). The analytical method used was validated in accordance with the European Medicines Agency guideline for bioanalytical method validation (EMEA/CHMP/EWP/192217/2009). Two hundred µl plasma was precipitated using methanol containing a stable isotope-labelled internal standard (naloxone d5). Precipitated samples were filtered using Impact protein precipitation plates (Phenomenex, Torrance, CA, USA). Analysis was performed using an Agilent 1260 LC system coupled to an Agilent 6460 QQQ detector (Agilent Technologies, Palo Alto, CA, USA). Separation was performed on a Phenomenex Kinetex EVO C18 (100 × 3.0 mm × 2.6 µm) column. Quality control samples analysed in duplicate at four levels of analyte were included in each analytical run. QC samples were prepared from pools of human plasma and spiked with naloxone at levels 0.05, 0.26, 15.32 and 38.5 ng/ml. The LOQ was < 0.02 ng/ml for 26 samples, < 0.05 ng/ml for 41 samples and < 0.1 ng/ml for 94 samples.

Drug supply

Nalokson DnE 14 mg/ml nasal spray was manufactured by AS Den norske Eterfabrikk (Oslo, Norway). Naloxon B. Braun 0.4 mg/mL (B. Braun Melsungen AG, Melsungen, Germany) was supplied from the Hospital Pharmacy in Trondheim, Norway.

Statistics and sample size

The significance level was set to 5%, and the sample size was scaled to not accept bioequivalence of an inferior or superior drug. The data used to assess the anticipated variation in the naloxone data were from previous studies of the same i.n. formulation. Based on this, it would be necessary to include 22 participants; see Supporting information for details. All planned analyses of the efficacy and safety variables were described in the Clinical Trial Analysis Plan. Analyses of variance (ANOVAs) were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

Pharmacokinetic calculations and simulations

Non-compartmental analysis (NCA) was applied assuming a salt factor of 1.0. Time zero concentration for i.n.- and i.m.-administered naloxone was set to zero, and for intravenous naloxone the first measured concentration was also used as concentration at time zero. The elimination rate constant (k_{el}) was assessed from at least three

concentrations in the semilogarithmic linear elimination phase. $AUC_{0\text{-last}}$ was assessed by the trapezoidal rule. $AUC_{0\text{-inf}}$ was calculated according to the following formula: $AUC_{0\text{-last}} + C_{last}/k_{el}$. Terminal half-life was calculated as $LN(2)/k_{el}$ and bioavailability (F) as $(AUC_{test,0\text{-inf}}/AUC_{reference,0\text{-inf}}) \times (Dose_{reference}/Dose_{test})$, where test was either i.n. or i.m. and reference either i.v.- or i.m.-administered naloxone. Clearance (CL) was calculated as $Dose \times F/AUC_{0\text{-inf}}$.

A non-parametric pharmacokinetic population model was developed for i.n. administration and one for i.m. administration, using Pmetrics version 1.5.0 (Laboratory for Applied Pharmacokinetics, Los Angeles, CA, USA) [19]. Details on model development, validation and simulation are presented in the Supporting information.

The population model was used to evaluate different dosing scenarios presented in Figs 2 and 4.

RESULTS

Patients

Forty-four subjects were screened and gave informed consent to participate. Twenty were not included, while 24 were randomized, two were withdrawn from the study after randomization: one because of an adverse event, and one started with medication, leading to exclusion. Twenty-two participants (12 men and 10 women) were included in the final analysis, all providing evaluable data from all four visits. The two participants who received the study drug and were later withdrawn were included in the safety analysis. Median age was 25.8 years (min = 20.7, max = 30.7) and a body mass index of median 22.5 kg/m^2 (min = 20.7, max = 26.0).

The mean time–course of the plasma concentrations (0–360 minutes) for the i.n., i.m. and i.v. administrations is seen in Fig. 1. As expected, the distribution and elimination phases are similar in all administrations, with both i.n. and i.m. staying above i.v. after 20 minutes. The real-data absorption phase is magnified in Fig. 2.1. The absorption rate of i.m. 0.8 is higher compared to i.n., but plasma concentrations following i.n. 1.4 mg and 2.8 mg administration surpass i.m. after 15 and 10 minutes, respectively. Figure 2.2 shows the simulated absorption phase, comparing i.n. 1.4 mg to both i.m. 0.4 mg and 0.8 mg. Concentrations after i.n. 1.4 mg exceeds concentrations after i.m. 0.4 mg after 7.5 minutes, and remains above (Figure 2.2).

C_{max} (Table 1) was significantly different between the three administration routes ($P = 0.03$, ANOVA); however, i.m. 0.8 mg and i.n. 1.4 mg did not differ significantly [$P = 0.72$, Tukey's honestly significant difference (HSD)]. There was no interaction of treatment sequence on C_{max} ($P = 0.90$, ANOVA).

$AUC_{0\text{-last}}$ (Table 1) was significantly different between the three routes ($P = 0.0025$, ANOVA). Significant differences between both i.v. 0.4 mg and i.m. 0.8 mg ($P = 0.008$, Tukey's HSD) and i.n. 1.4 mg ($P = 0.050$, Tukey's HSD) were seen, but not between i.n. 1.4 mg and i.m. 0.8 mg ($P = 0.33$, Tukey's HSD). Treatment sequence

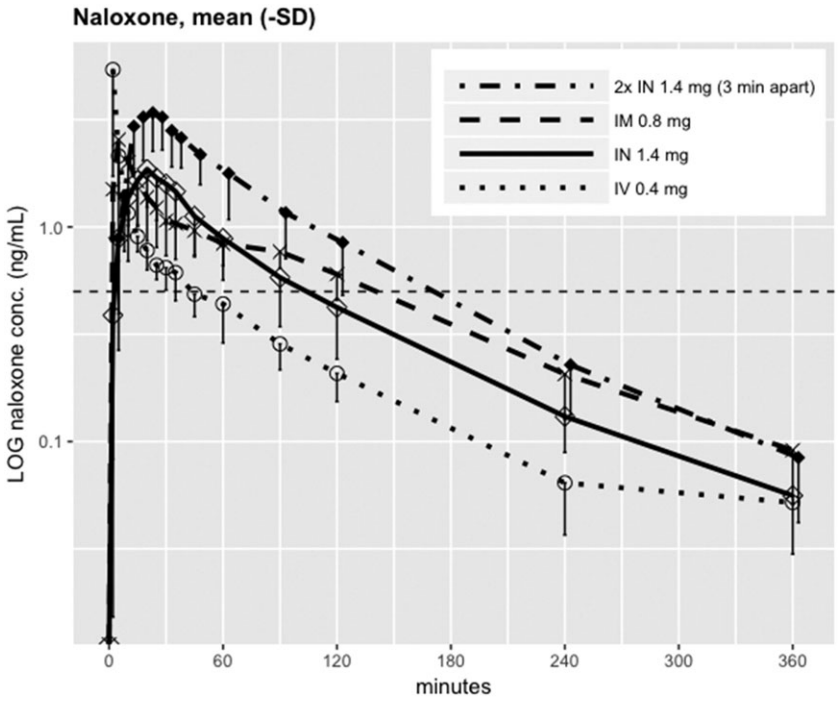

Figure 1 Time–course of plasma concentrations 0–360 minutes [mean ± standard deviation (SD)] of naloxone after intranasal (1.4 and 2.8 mg), intramuscular 0.8 mg and intravenous (0.4 mg) administration in healthy human volunteers ($n = 22$). Dashed horizontal line indicates 0.5 ng/ml, a proposed minimum effective concentration in the elimination phase

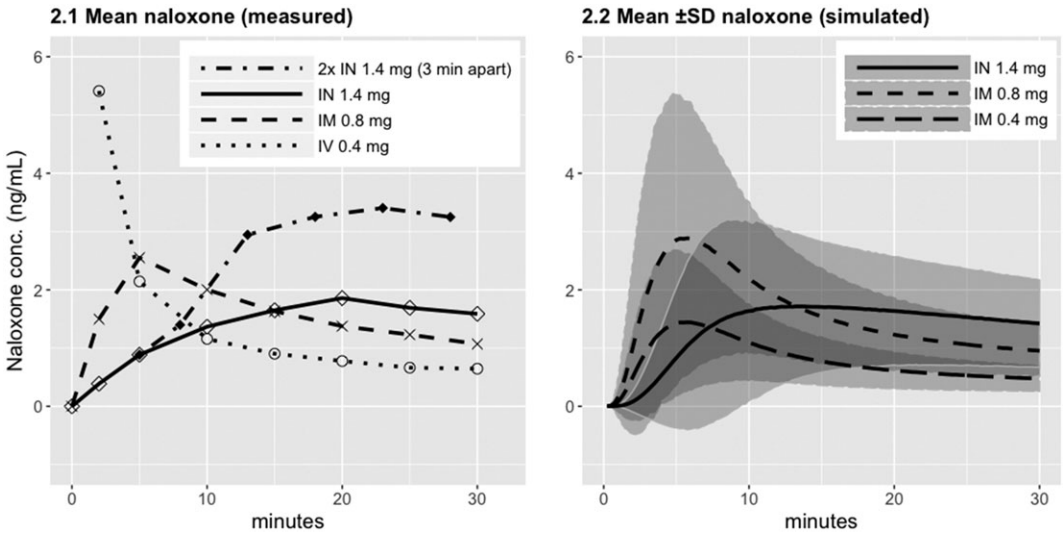

Figure 2 2.1: Time–course of plasma concentrations 0–30 minutes (mean values, variability removed for clarity) of naloxone after intranasal (i.n.) (1.4 and 2.8 mg), intramuscular (i.m.) 0.8 mg and intravenous (0.4 mg) administration in healthy human volunteers (n = 22). 2.2: Simulated time–course of plasma concentrations 0–30 minutes [mean ± standard deviation (SD) as shaded area] of naloxone after i.n. 1.4 mg and i.m. 0.4 mg and 0.8 mg

Table 1 Pharmacokinetic variables (mean values ± SD) n = 22 healthy volunteers after intranasal, intravenous and intramuscular administration of naloxone in an open, randomized four-way cross-over trial.

Treatment	C_{max} *(ng/ml)*	T_{max} *(min)*	AUC_{last} *(h × ng/ml)*	$AUC_{0\text{-}inf}$ *(h × ng/ml)*	*Terminal half-life (min)*	*Cl (L/h)*
1.4 mg i.n.	2.36 ± 0.68[§]	20.2 ± 9.4[§]	2.62 ± 0.94[§]	2.84 ± 0.94[§]	73.0 ± 20.2[§]	239 ± 68
2.8 mg i.n.	4.18 ± 1.53	20.7 ± 9.54	5.23 ± 1.79	5.47 ± 1.89	69.8 ± 12.8	250 ± 66
0.8 mg i.m.	3.73 ± 3.34	13.6 ± 15.4	3.09 ± 0.64	3.43 ± 0.66	84.8 ± 26.5	236 ± 68
0.4 mg i.v.	7.44 ± 9.67	3.5 ± 4.2	1.84 ± 1.49	2.09 ± 1.47	74.3 ± 32.1	223 ± 58

C_{max} = maximum concentration; T_{max} = time to maximum concentration; AUC_{last} = area under the curve until last measurement; $AUC_{0\text{-}inf}$ = area under the curve until infinity; Cl = clearance. Intranasal (i.n.) 2.8 mg is administered as i.n. 1.4 mg naloxone 3 minutes apart in the same nostril; [§]not statistically significant different to intramuscular (i.m.) 0.8 mg ($P > 0.05$). SD = standard deviation; i.v. = intravenous.

did not show any significant interaction with the effect (P = 0.80, ANOVA). Data analysed as $AUC_{0\text{-}inf}$ showed similar differences to the $AUC_{0\text{-}last}$ data, but in these data i.v. 0.4 mg and i.n. 1.4 mg only tended to be significantly different (P = 0.059, Tukey's HSD). The applied sampling strategy assured coverage of 92 ± 6%, 96 ± 2%, 90 ± 8% and 87 ± 11% of the systemic exposure of $AUC_{0\text{-}last}$, compared to $AUC_{0\text{-}inf}$ for i.n. 1.4 mg, 2 × i.n. 1.4 mg, i.m. 0.8 mg and i.v. 0.4 mg, respectively.

T_{max} (Table 1) was not significantly different between i.m. 0.8 mg and i.n. 1.4 mg (P = 0.098, t-test). Mean time to 50% of C_{max} was 10.1 minutes for i.n. 1.4 mg naloxone and 6.5 minutes for i.m. 0.8 mg (P = 0.061, t-test). On average, naloxone concentrations following both i.n. 1.4 mg and i.m. 0.8 mg were above 0.5 ng/ml at the first sample at 2 minutes (Fig. 2).

Mean terminal elimination half-lives (Table 1) of naloxone ranged from 73 to 85 minutes, and were not significantly different between the different administration forms (P = 0.11, ANOVA). In the elimination phase, 0.5 ng/ml has been suggested as a minimum effective concentration of naloxone [20]. Figure 1 shows how i.n. 1.4 mg maintained its concentration above this for 88 minutes and i.n. 2.8 mg for 118 minutes, i.n. 0.8 mg for 118 minutes and i.v. 0.4 mg for 45 minutes.

The absolute bioavailability for i.n. 1.4 mg in this study was 0.49 ± 0.24, while the relative bioavailability to i.m. 0.8 mg was 0.52 ± 0.25 (Figure 3).

Dose proportionality assessed by systemic exposure ($AUC_{0\text{-}last}$) between i.n. 1.4 mg and 2 × i.n. 1.4 mg naloxone was, on average, 1.09 ± 0.53 and for C_{max} 1.27 ± 0.57.

Results from PK simulations

A two-compartment model with five transit compartments in the absorption phase described the data well. The model was parameterized using differential equations with rate constants and volume of distribution in the

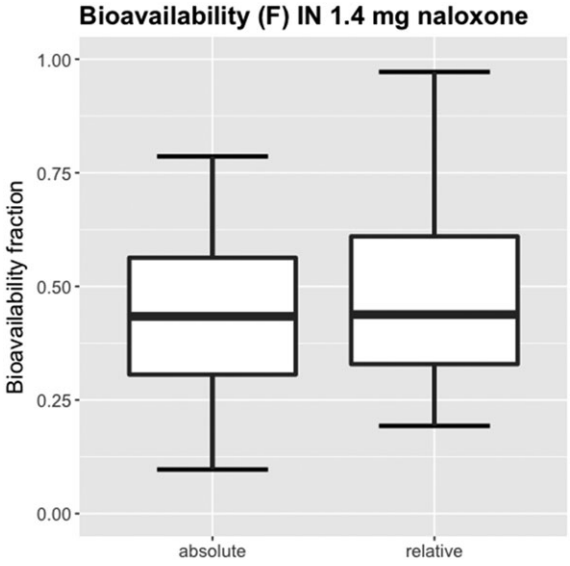

Figure 3 Box-plot of absolute and relative bioavailability of intranasal 1.4 mg naloxone. Bold line is median, box is 75% percentiles and whiskers are 95% percentiles

central compartment, scaled for centralized (median) body weight. No covariates were retained in the final models. The i.n. and i.m. models had 42 and 41 support points, respectively. A more detailed presentation of model development and validation is shown in the Supporting information.

Simulations

Simulation of the absorption phase in a 'standard' person weighing 70 kg from the respective population pharmacokinetic model, i.e. the i.n. and i.m. models separately, is presented in Fig. 2.2; i.m. administration is simulated as 0.8 mg and 0.4 mg. The major observation is that the lag in achieved plasma concentrations during the absorption phase between i.n. 1.4 mg and i.m. 0.4 mg is, as expected, far smaller than when compared with i.m. 0.8 mg.

The model is used to visualize clinical scenarios where 1.4 mg i.n. naloxone is administered prior to, or in addition to, injected naloxone.

Figure 4.1 shows i.n. 1.4 mg naloxone administered 10 minutes prior to injected i.m. naloxone, a common scenario in THN. Plasma concentrations following i.n. 1.4 mg remain above the concentrations obtained by i.m. 0.4 mg during the whole period. They do not reach the levels obtained by i.m. 0.8 mg within this 20-minute period. Figure 4.2 simulates the shortest time that i.n. 1.4 mg could be administered prior to i.m. 0.4 mg, and constantly provides higher plasma concentrations. That time is 2.25 minutes. Figure 4.3 simulates the opposite; the injection of i.m. 0.4 mg naloxone, 10 minutes after i.n. 1.4 mg is given. The C_{max} in this scenario is 3.15 ng/ml, a lower C_{max} than what we find for i.m. 0.8 mg in our real data.

Safety and adverse events

At anterior rhinoscopy at the follow-up visit, one had abnormal colour and swelling of mucosa, one had abnormal amount and colour of secretion and one had presence of concha inferior swelling, not present prior to the study. One participant had a clinically significant increased value of ALT after treatment with i.n. 1.4 mg, and was withdrawn. This increase of the ALT value was deemed possibly related to the study drug. A total 31 adverse events were reported for 14 participants in the study. All adverse events reported were of mild severity except for one abnormal haemoglobin, which was reported as moderate, but unrelated to treatment. The adverse events reported most by participants were headache and nasal congestion. For questions related to irritation in the nose, no events were reported for rhinorrhoea, itching and loss of smell

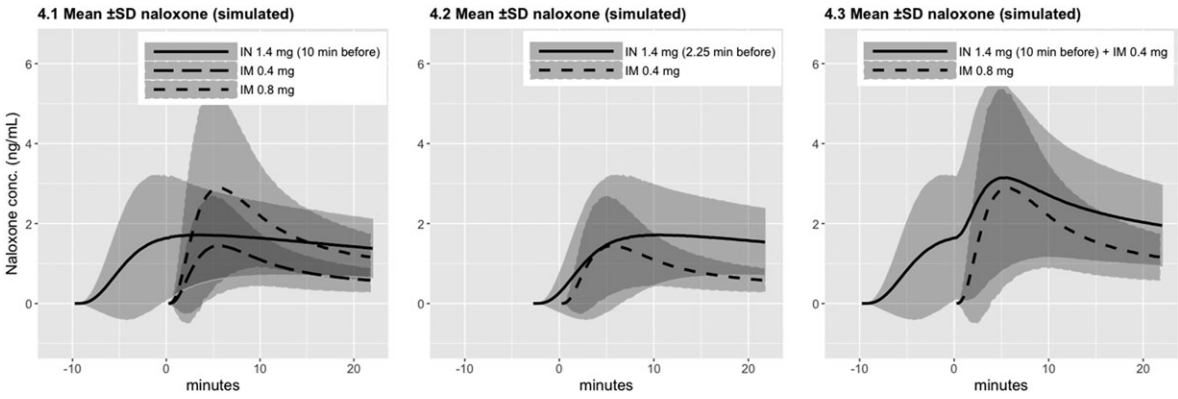

Figure 4 Simulated time–courses of mean naloxone concentrations (line) and standard deviations as shaded area. 0 minutes indicate a time of administration of injected naloxone.4.1 shows intranasal (i.n.) 1.4 mg naloxone administered 10 minutes prior to injected naloxone (0.4 and 0.8 mg); 4.2 shows the simulation of the shortest time (2.25 min) beneficial to give i.n., rather than wait for naloxone to be injected; 4.3 simulates a situation where intramuscular (i.m.) 0.4 mg naloxone is injected to a patient already given i.n. 1.4 mg 10 minutes previously

sensation; i.n. administration of 1.4 mg naloxone was found to be safe and well tolerated by healthy volunteers.

DISCUSSION

The major finding in this study was that the absorption of 0.8 mg naloxone administered i.m. was slightly faster than for the i.n. 1.4 mg. There were no statistically significant differences between i.n. 1.4 mg and i.m. 0.8 mg in $C_{max,}$ $T_{max,}$ or $AUC_{0\text{-last}}$. Intranasal naloxone showed a dose linear increase in systemic exposure for two doses to the same nostril separated by 3 minutes, indicating that it is suited for repeated administration and titration. Simulations showed that i.n. 1.4 mg naloxone compares well with 0.4 mg i.m. naloxone, providing higher concentrations within 7.5 minutes. The present i.n. formulation was safe in healthy volunteers, and has received regulatory approval in 12 European countries under the trade name Ventizolve® (Respinal® in Sweden).

This study builds on two previously published studies of a similar naloxone formulation [16,17]. The formulation shows a similar dose-corrected C_{max} across these studies. The absolute bioavailability was also similar, but the relative bioavailability compared to i.m. was lower compared to when naloxone was given together with remifentanil [17].

Several new naloxone formulations have come to the market in recent years. Nyxoid 1.8 mg i.n. naloxone by Mundipharma (Cambridge, UK) [21] and Narcan Nasal 2.0 mg and 4.0 mg i.n. naloxone (Adapt Pharma, Inc., Radnor, PA, USA) [22] are now available. These formulations and the present 1.4 mg have several pharmacokinetic characteristics in common. They can all deliver a therapeutic dose (corresponding to 0.4–2.0 mg i.m.) by one actuation of a 0.1 ml volume by the Aptar Unit dose device. They all have a relative bioavailability of about 50%, a similar average T_{max} of 21 minutes (min = 15, max = 30) and a similar dose-corrected C_{max} (1.52 ± 0.16 ng/ml, n = 9). Although the absolute C_{max} of i.n. 1.4 mg was 82 and 76% of Nyxoid and Narcan, respectively, i.n. 1.4 mg C_{max} was 186% compared to that of 0.4 mg i.m. [21]. $AUC_{0\text{-inf}}$ for i.n. 1.4 mg was 85% of that of i.m. 0.8 mg, but again this exceeds by far the published AUC values of 0.4 mg i.m. (157 and 134%) of Narcan Nasal and Nyxoid, respectively.

Questions have been raised about different uptake and interactions with opioids or other drugs used by patients in overdose. In a previous study of this i.n. naloxone formulation administered with the opioid remifentanil, the relative bioavailability to i.m. was 75% [17]. This led to the conclusion that there may be an interaction between naloxone and remifentanil. Further studies in this direction can bridge the gap between healthy volunteers and patients presenting with opioid overdose.

The current formulation was compared with i.m. 0.8 mg naloxone as reference, as it represents the safe upper end of the starting dose recommendations, without undue risk of triggering withdrawal. As other regulatory studies relate to 0.4 mg i.m., a population kinetic simulation was developed to examine the relations between 1.4 mg i.n. and 0.4 mg i.m. Modelling is also used to compare different treatments in a THN scenario, where peer-administered naloxone may substitute or be combined with injected naloxone by ambulance personnel. Titration is the core principle in naloxone reversal of overdose, and these simulations can guide clinical use. Part of the rationale of THN is to shorten the time from when an opioid overdose is suspected to the administration of antidote. Calling for help, dispatch and transport times for ambulance personnel, securing the work-place, establishing airway and breathing control and preparing and injecting naloxone takes considerable time. As shown in Fig. 4.1, when naloxone was given 10 minutes prior to naloxone injected, the THN administration of the present formulation delivered serum concentrations above i.m. 0.4 mg at all times, although below i.m. 0.8 mg. Calculations showed that when i.n. 1.4 mg was given as closely as 2.25 minutes before i.m. injection of 0.4 mg, it still provided higher blood concentrations (Fig. 4.2). This indicates a clinical benefit by this i.n. formulation, even by ambulance personnel, as 2.25 minutes is comparable to the time it takes to prepare an i.m. injection site, fill a syringe and inject naloxone or to establish i.v. access [23]. Figure 4.3 shows a simulation where ambulance personnel administer 0.4 mg i.m. naloxone 10 minutes after 1.4 mg is given as THN. This would be relevant if a patient remained unresponsive after one dose i.n., and ambulance personnel suspected opioid intoxication to be a possible cause. The C_{max} in this scenario is almost identical to the arithmetic mean of Nyxoid 1.8 mg, and is reached 5 minutes after ambulance personnel-administered i.m. naloxone. The early administration of antidote is the rationale behind THN, and the simulations show that i.n. 1.4 mg has a place in this treatment model and is well suited for titration.

The safe initial dose of naloxone is debated [12], and will remain a balancing act between safe reversal and the precipitation of acute withdrawal reactions [4]. Dilute formulations have shown to provide a relatively low rate of repeat naloxone dosing in the field [24–26]. Previously approved nasal formulations deliver systemic exposure similar to 1.0 and 2.0 mg injected naloxone, which is above the upper initial dose recommended by the WHO [2]. A high initial dose will increase the likelihood of provoking acute withdrawal; the symptoms are well described [27], and experiencing withdrawal is feared among opioid abusers [28]. Withdrawal and inadequate follow-up may lead to death [29]. Withdrawal is a part of what leads to early discharge or being left at the scene against medical

advice. Both must be seen as less than ideal follow-up after non-fatal overdoses. Being left at the scene of the overdose has been debated over the years and found to be relatively safe, as death immediately afterwards is rare [30,31]. This may change in future with the arrival of more potent opioids, and vary between the location and other circumstances of the overdose [32]. There is conflicting evidence regarding the fentanyl-like opioids and the need for potent naloxone formulations [33,34], but basic first aid with ventilation and antidote titration will remain the treatment gold standard.

Limitations

This is study is conducted in healthy volunteers who may differ from patients being treated for opioid overdose. Our participants did not use concomitant medication, so interactions with other drugs, prescription or illegal, are not assessed. The conclusions in this study are based on plasma concentrations, not relevant clinical end-points.

CONCLUSION

Intranasal 1.4 mg naloxone provides adequate systemic concentrations compared to i.m. 0.8 mg, without statistical differences concerning maximum plasma concentration, time to maximum plasma concentration or area under the curve. The naloxone exposure following administration by this formulation far exceeds the more dilute 'off-label' formulation often used in THN programmes. Compared to the higher doses in other nasal sprays, i.n. 1.4 mg can reduce the risk for withdrawal, while still safe, as it reaches relevant plasma concentrations swiftly. It exceeds i.m. 0.4 mg after 7.5 minutes. Simulations support that it has a place both as a peer-administered antidote and for titration of treatment by professionals. However, only randomized clinical trials on real opioid overdoses can determine whether i.n. naloxone can compare with i.m. naloxone.

Declaration of interests

The formulation described has been approved by 12 European countries from 16 June 2018 under the name of Ventizolve® (Respinal® in Sweden), produced by Sanivo Pharma AS. The sponsor of this trial was AS Den Norske Eterfabrikk. O.D. was engaged by AS Den Norske Eterfabrikk as Principle Investigator in this study, for which O.D. receives no personal honorarium. O.D.'s employer Norwegian University of Science and Technology (NTNU) and its subsidiary Technical Transfer Office have signed cooperation and licensing contracts with DNE PHARMA to seek commercialization of this nasal naloxone formulation. This regulates potential royalties for OD through NTNU. DNE PHARMA AS has compensated O.D. for business travel from Trondheim to Oslo. A.K.S. has signed a non-compete contract with AS Den Norske Eterfabrikk lasting the duration of his PhD programme at NTNU (estimated 2018). This does not limit A.K.S.'s right to publish results. A.K.S. has received no honorarium from AS Den Norske Eterfabrikk or DNE PHARMA AS, and will receive no financial benefit from the licence agreement between DNE PHARMA AS and NTNU. A.Å has received a consultant honorarium from DNE PHARMA in relation to the naloxone formulation presented.

The other authors declare they have no conflicts of interest.

Acknowledgements

The authors thank the Clinical Research Facilities at St Olav's University Hospital and Oslo University Hospital for conducting the study, and to the participants for giving their time. We also thank Øyvind Danielsson Glende for his valuable work in the early phase of this study [Correction added on 21 February 2019, after first online publication: The Acknowledgements have been updated in this version.].

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 Parameter values for the final intranasal model.
Table S2 Parameter values for the final intramuscular model.
Figure S3 OP-plot intranasal.
Figure S4 OP-plot intramuscular.
Table S5 Median validation statistics for internal and external validation of the final models.